PATENT
Docket No.: **19603/3541 (CRF D-2694-02)**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Hyman et al.	)	Examiner:
			)	Amanda L. Lauritzen
Serial No.	:	10/001,643	)	
			)	Art Unit:
Cnfrm. No.	:	2817	)	3737
			)	
Filed	:	October 31, 2001	)	
			)	
For	:	IN VIVO MULTIPHOTON DIAGNOSTIC DETECTION AND IMAGING OF A NEURODEGENERATIVE DISEASE	)	

REQUEST FOR RECONSIDERATION

Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Applicants respectfully request reconsideration of the January 3, 2008, office action.

The rejection of claims 1-5, 8-14, 16, 18-21, 24-30, 32, 34, 36, and 38-40 under 35 U.S.C. § 103(a) for obviousness over U.S. Patent No. 6,329,531 to Turner et al. ("Turner") in view of U.S. Patent Application Publication No. 2003/0236458 to Hochman (" Hochman") is respectfully traversed.

As demonstrated in the accompanying Declaration of Watt Webb, Sc.D. under 37 C.F.R. § 1.132 ("Webb Declaration"), Dr. Webb is an expert in the art (Webb Declaration ¶¶ 1-5) and, in his opinion as an expert, the claimed invention is nowhere suggested by the above-noted references (Webb Declaration ¶¶ 8-11).

Turner relates to *in vivo* and *in vitro* diagnosis of neurodegenerative diseases such as Alzheimer's Disease by means of near infra-red radiation (Webb Declaration ¶ 8). According to the *in vivo* methods of Turner, one or more dye compounds are fed to the tissue being

diagnosed and light from the near-infrared spectral region is irradiated (*Id.*). The non-absorbed, scattered light and/or scattered fluorescence radiation emitted by the dye is recorded simultaneously/individually (*Id.*). Preferred methods are where the tissue irradiates over a large surface, and the fluorescence radiation that is resolved locally is visualized by imaging with a CCD camera or the tissue areas that are to be imaged are rastered with a fiber optic light guide and the signals that are received are converted numerically into a synthetic image (*Id.*). Fluorescence can also be evaluated spectrally and/or by phase selection, as well as in a steady-state manner and/or in a time-resolved manner (*Id.*).

Hochman teaches methods for optically detecting physiological properties in an area of interest by detecting changes in the intrinsic or extrinsic optical properties of tissue (Webb Declaration ¶ 9). This involves optically detecting blood flow changes, blood characteristics, and blood vessel abnormalities, as well as determining the presence and location of abnormal or pathological tissue for identifying and mapping the margins of abnormal tissue (*Id.*). According to Hochman, these methods may be used to identify physiological conditions associated with and to evaluate diagnosis of Alzheimer's Disease and other neurodegenerative disorders (*Id.*). Optical detection may involve invasive or semi-invasive systems and may be continuous or non-continuous (*i.e.*, pulsed) (*Id.*). Data sets from patients can be compared to standard or control data representative of optical properties indicative of various disease states or conditions (*Id.*). Longer wavelengths (e.g., approximately 800 nm) can be employed to analyze deeper areas of tissue (*Id.*).

Turner and Hochman disclose the use of a class of colorant signal molecules (Webb Declaration ¶ 10). To the extent these references discuss how they are used, their achievement of fluorescent excitation does not result in a non-linear process like two-photon or multiphoton excitation (*Id.*). The dyes utilized by Turner and Hochman absorb low-energy infrared radiation photons to excite the dye molecules to the low energies corresponding to the infrared photons (*Id.*). In contrast, two-photon or multiphoton excitation absorbs two or more infrared photons virtually simultaneously to excite a molecule to an energy level corresponding to the sum of the energies of the two or more infrared photons (*Id.*). These energy levels can then be high enough to be released by emission of visible or even ultraviolet fluorescence (*Id.*). Since the procedures used by Turner and Hochman do not achieve such a high energy of

excitation, it is apparent that they do not carry out simultaneous multiphoton excitation, in accordance with the present invention (*Id.*).

Thus, neither Turner nor Hochman teach or suggest the method of the present invention involving activating brain tissue of a mammal by application of radiation through an opening or a thinned portion of the mammal's skull to promote simultaneous multiphoton excitation, where the radiation is pulsed at a pulse width between about 10^{-9} to 10^{-15} second (Webb Declaration ¶ 11). Since neither of the cited references teaches these aspects of the claimed invention, their combination cannot do so either. It is, therefore, apparent (contrary to what is said in the outstanding office action) that applicants are not simply arguing how the cited references individually fail to teach the claimed invention. In view of Dr. Webb's expert opinion that neither Turner nor Hochman utilize simultaneous multiphoton excitation, the unsupported statements in the final rejection to the contrary are clearly wrong. For example, the U.S. Patent and Trademark Office's ("PTO") assertion that Hochman "teaches multiphoton excitation in diagnosis of the same diseases claimed" is clearly incorrect. Similarly, the statement by the PTO that Turner discloses "a method for detecting a neurodegenerative disease comprising activating brain tissue by application of radiation under conditions to promote simultaneous [multi]photon excitation" is also not accurate. In view of Dr. Webb's impressive credentials in the field and the lack of any evidence demonstrating that this conclusion is wrong, there is no sound basis to rely on Hochman and Turner to reject the claims.

Accordingly, the rejection of claims 1-5, 8-14, 16, 18-21, 24-30, 32, 34, 36, and 38-40 under 35 U.S.C. § 103(a) for obviousness over these references is improper and should be withdrawn.

In view of all of the foregoing, applicants submit that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

Date: December 31, 2008

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